REMARKS

It is noted that the claims have been rejected only on formal grounds. However, to assist understanding of the subject matter being claimed, it is believed helpful to consider the background prior art.

It has been known at least since 1968-70 that gas microbubbles can be used as an imaging agent in contrast echocardiography, also referred to as ultrasonic imaging. In the intervening years, the ultrasonic imaging art has sought to improve three inter-related parameters: bubble size, stability, and concentration. The objective was to obtain a highly concentrated bubble population of greater size and uniformity, and of smaller diameter together with enhanced stability.

Hilmann, et al. (AA) illustrates the objectives of reducing microbubble size and improving microbubble stability. This reference discloses microbubbles of less than 50 microns which were stable for around two minutes.

Tickner, et al. (AB) describes microbubbles which are stabilized by captivation in solidified gelatin. A desirable size range of 0.5 to 300 microns is disclosed, but the sole example describes microbubbles of 38, 80 and 140 microns. No method is disclosed for producing smaller bubbles.

The Tickner, et al. publication of 1970 (AR-1) also relates to gelatin-captivated microbubbles. A study of bubble diameter (Fig. 6-2, page 39) indicated bubble sizes of 120 to 210 microns. No stability data is presented. On page 37 it is stated that "gelatin coated bubbles do not tend to coalesce as do uncoated ones", and that "this observation is true for periods of time of the order of minutes after dissolution of the mass", referring to the gelatin-captivated bubbles.

The art was advanced by the invention disclosed in Feinstein Patent 4,572,203 (AC). By sonication of a biocompatible liquid, preferably a viscous liquid, microbubbles are produced having substantially uniform diameter, viz. from about 6 20 microns.

The Feinstein et al. publication of 1984 (AS-1) presents related data. It was shown that a population of microbubbles of less than 10 microns can be produced by sonication of sorbitol or dextrose solutions, and that the resulting microbubbles had stabilities of the order of around 180 seconds (Table 2, page 18).

A further advance in this art is disclosed in Feinstein Patents 4,718,433 (AD) and 4,774,958 (AE). The microbubble ultrasonic imaging agent of those patents is formed from a protein solution by subjecting the solution to sonication while heating it sufficiently to denature portions of the protein. A population of microbubbles of diameters less than 9 microns is produced. As described in the last paragraph of column 4 and illustrated by Fig. 2, the microbubble concentration can be 10 million microspheres (10^7) per milliliter (last par., col. 4, and Fig. 2). The stability was up to 48 hours (col. 4, lines 31-32). This imaging agent was tested for heart imaging as described in Keller, et al. (AT-1). Left ventricular opacification was obtained following peripheral venous injection of the contrast agent. The microbubbles were of sufficiently small size and persistence for transpulmonary passage.

A further invention had to be made to achieve diagnostic and commercial practicality. The sonicated protein solution microbubbles of Feinstein were storage stable for only a few days. They could not be manufactured and distributed to hospital laboratories.

The next advance in this art was made by the inventors of the application as described herein. The applicants are employees of Molecular Biosystems, which is the exclusive licensee of the three Feinstein patents described above.

The imaging agent of this invention comprises microspheres which consist of gas bubbles enclosed by solid walls of heat-insolubilized biocompatible materials. They are characterized by the physical properties of size, concentration, and stability.

The microspheres in applicants' imaging agent are predominately of diameters less than 10 microns, are present in concentrations of greater than 1 x 10^8 microspheres per milliliter, and are stable in the medium as evidenced by maintaining a concentration of over 10^8 microspheres per milliliter when stored for at least 4 weeks at a temperature of at least 20 to 25C.

Claim Terminology

The claims have been rewritten to improve their form. It is believed that the rewritten claims may properly employ the terminology used. The claims are not unduly broad or functional when read in the light of the specification and considered in relation to the background prior art. Terminology similar to that criticized in the action has been considered acceptable for this kind of subject matter.

The claims of Hilmann, et al. (AA) are illustrative. They cover "tenside" as a component of "an aqueous intravenously injectable physiologically acceptable aqueous carrier liquid". Additional components are "at least one viscosity-raising compound", and "a physiologically acceptable sterile gas for forming microbubbles".

Tickner, et al. claimed an ultrasonic imaging agent having "a coalescence resistant surface membrane encapsulating a gas of selected composition". The membrane material is further claimed as "a gellable composition".

Feinstein (AC) claimed "injecting biodegradeable, metal-containing microparticles" (claim 1), and also sonication of "a biocompatible liquid" (claim 7), or "a viscous solution" (claim 10).

In Feinstein (AD), the improvement was defined in claim 1 as "forming an aqueous protein solution, subjecting said solution to high frequency sonication while heating the solution sufficiently to denature portions of the protein". The claims of Feinstein (AE) are of similar broad scope.

It is respectfully submitted that the claims in this application should not be treated differently from the prior inventions in the microbubble imaging art. The rewritten claims are based on the specification disclosure, and define the improvements of this invention in relation to the closest prior art.

There is no criticality in the gas used to form the microbubble, the reflection of the sound waves being a property of gases generally. For simplicity, air is preferred, but any parenterally administerable gas can be used (nitrogen, oxygen, carbon dioxide, etc.). This is in accordance with the disclosures of the specification and the prior patents.

In view of the prior art and the specification disclosure, applicants should be permitted to cover microspheres having walls formed from "heat-insolubilized biocompatible material". While a heat-sensitive protein is preferred, and for administration to humans human serum albumin advantageous, the invention is not limited to any specific biocompatible material.

The Examiner has referred to the method disclosed for preparing the imaging agent. However, the claims are product claims, and the product is defined independently of any specific process for producing it. In order to claim a new composition of matter, it is only necessary to disclose one method of producing it. Other methods can be used while obtaining the same product. The batch procedure described in the application has been scaled up for continuous production by Molecular Biosystems.

The definition of stability is in terms of a reference standard. The fact that the microspheres have been stabilized in accordance with the present invention is evidenced by the fact that they maintain a concentration of greater than 1×10^8 microspheres per milliliter when stored for over 4 weeks. This description is definite and non-functional.

Further consideration of the allowability of claims 11 to 18 is requested.

Respectfully submitted,

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